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Prenatal exposure to per- and polyfluoroalkyl substances (PFAS) from contaminated water and risk of childhood cancer in California, 2000–2015

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Background: Few studies have investigated associations between per- and polyfluoroalkyl substances (PFAS) and childhood cancers. Detectable levels of PFAS in California water districts were reported in the Third Unregulated Contaminant Monitoring Rule for 2013–2015.

Methods: Geocoded residences at birth were linked to corresponding water district boundaries for 10,220 California-born children (aged 0–15 years) diagnosed with cancers (2000–2015) and 29,974 healthy controls. A pharmacokinetic model was used to predict average steady-state maternal serum concentrations of perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) from contaminated drinking water. Adjusted odds ratios (AORs) and 95% confidence intervals (CIs) per doubling of background exposure were calculated for cancers with at least 90 cases.

Results: Predicted PFOS and PFOA maternal serum concentrations ranged from background (5 ng/ml PFOS and 2 ng/ml PFOA) to 22.89 ng/ml and 6.66 ng/ml, respectively. There were suggestive associations between PFOS and nonastrocytoma gliomas (n = 268; AOR = 1.26; 95% CI: 0.99, 1.60), acute myeloid leukemia (n = 500; AOR = 1.14; 95% CI: 0.94, 1.39), Wilms tumors (n = 556, AOR = 1.15; 95% CI: 0.96, 1.38), and noncentral system embryonal tumors (n = 2,880; AOR = 1.07; 95% CI: 0.98, 1.17), and between PFOA and non-Hodgkin lymphoma (n = 384; AOR = 1.19; 95% CI: 0.95, 1.49). Among children of Mexico-born mothers, there was increased risk of Wilms tumor (n = 101; AOR_{PFOS} = 1.52; 95% CI: 1.06, 2.18; AOR_{PFOA} = 1.59, 95% CI: 1.12, 2.24) and noncentral system embryonal tumors (n = 557; AOR_{PFOS} = 1.24, 95% CI: 1.03, 1.50; AOR_{PFOA} = 1.19, 95% CI: 0.98, 1.45).

Conclusion: Results suggest associations between predicted prenatal maternal PFAS serum concentrations and some childhood cancers. Future analyses are warranted.

Keywords: Per- and polyfluoroalkyl substances; PFAS; PFOA; PFOS; Childhood cancer; Drinking water

Introduction

Per- and polyfluoroalkyl substances (PFAS) are synthetic chemicals that are ubiquitous in nature following their use in manufacturing and consumer products since the 1940s, causing a public health concern. Approximately 98% of the United States (US) population has detectable PFAS in their blood, as determined by the US Centers for Disease Control and Prevention.[1] While perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS) use was largely ceased in the US in the 2000s, the chemicals remain in the environment due to their stability and long half-lives.[1] Drinking water and diet are the main sources of PFAS exposure in adults, and these exposures can be passed down to children during pregnancy and breastfeeding.[1–3] As of April 2024, the Environmental Protection Agency (EPA) has finalized the first nationwide drinking water standard that sets the legally enforceable level, or maximum contaminant level of PFOS and PFOA to 4 ng/l.[4–6]

PFAS have been detected in water systems across the country. The Safe Drinking Water Act requires the EPA to monitor unregulated contaminants in public water systems serving more than 10,000 people, as well as in a representative sample of 800 smaller water systems. In the Third Unregulated Contaminant

What this study adds:
The literature regarding per- and polyfluoroalkyl substances (PFAS) exposures and childhood cancers is sparse. Other studies have linked prenatal PFAS exposures to childhood leukemia and retinoblastoma. This research is also one of the first analyses of childhood cancer risk associated with PFAS exposures via drinking water contamination. PFAS contamination in water is a modifiable exposure that was recently the subject of policy implementations in the Environmental Protection Agency's PFAS National Primary Drinking Water Regulation. Analysis of this exposure source provides insights on the potential health impacts of the policy.

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Monitoring Rule (UCMR3), 30 contaminants were required to be monitored from 2013 to 2015 including PFOA, PFOS, perfluorobutanesulfonic acid, perfluoroheptanoic acid, perfluorohexanesulfonic acid, and perfluorononanoic acid.[7] A total of 194 public water systems in 33 states reported detectable PFAS levels, with the greatest number of detections above minimum reporting levels (20 ng/l for PFOA, 40 ng/l for PFOS) in California.[8] For PFOA and PFOS specifically, it is estimated that 6 million people were exposed through their public water systems, with 66 public water systems having at least one detection above the USEPA 2016 health advisory level of 70 ng/l of PFOS or PFOA individually or combined.[8] These minimum reporting levels and health advisory levels are an order of magnitude larger than that of the finalized maximum contaminant level for PFOS and PFOA at 4 ng/l.

Evidence supporting the carcinogenicity of PFOA and PFOS is growing. PFOA and PFOS have been classified as group 1 ("carcinogenic to humans") and group 2B ("possibly carcinogenic to humans"), respectively, by the International Agency for Research on Cancer in 2023,[9] based upon animal studies and mechanistic evidence in humans. These analyses determined that there was "limited evidence" for renal cell carcinoma (RCC) and testicular cancer from PFOA exposure, as well as "strong" mechanistic evidence for both PFOA and PFOS.[9] Epidemiologic evidence to date has been somewhat sparse: in a recent review of PFAS and cancer in humans, testicular and kidney cancers were most consistently associated with PFAS exposure,[10] along with sporadic positive findings for cancers of the breast, prostate, liver, colorectal, bladder, and hematopoietic cancer. However, the epidemiologic studies of PFAS and cancer included in the scoping review had methodologic challenges, including low variation in PFAS exposure, differences in exposure assessment (e.g., measured serum, modeled serum, job characterization, water exposure characterization), selection bias, unknown/unmeasurable duration of exposure, and power/sample size issues,[10] which simultaneously may not only create spurious associations but also mask the true association that exists.

Fewer studies have explored the relationships between PFAS exposures and childhood cancer risk. One recent study found a positive association between PFOS and PFOA levels measured in newborn dried blood spots and retinoblastoma in children born in California.[11] Additionally, another study identified a positive association between acute lymphoblastic leukemia and *N*-methyl-perfluorooctane sulfonamidoacetic acid levels measured in maternal pregnancy serum in the Finnish Maternity Cohort.[12] While initial analyses suggested a positive association with maternal serum PFOS in a subset of the samples from earlier study years, no overall association was found.[12] Clusters of childhood cancers such as leukemia, brain tumors, and rhabdomyosarcoma were observed in regions near PFAS-contaminated sites.[13–15] Generally, the incidence of several childhood cancer subtypes in the US has risen over recent decades, indicating the potential involvement of environmental factors in their etiology.[16–20]

The objective of this study was to examine the association between predicted PFOS and PFOA concentrations in prenatal maternal serum, utilizing exposure measures derived from potential drinking water consumption, and the odds of childhood and adolescent cancer in California from 2000 to 2015. We analyzed individual-level data for the incidence of specific cancer types and estimated individual exposures to PFOS and PFOA based on reported concentrations from the UCMR3 data for California water systems.

Methods

Study population

The study population consisted of cases and controls from the California Linkage Study of Early-onset Cancers (CALSEC), a statewide study linking data from the California Cancer Registry (1988–2015) with California birth data from the Center for Health Statistics and Informatics (1978–2015). Details of the CALSEC study design and sample collection have been published previously.[21–23] For this analysis, we focused on cases diagnosed at age 0–15 years (n = 10,220) and controls (n = 29,974) born in California between 2000 and 2015 with available geocoded birth addresses. This sample excludes an additional 165 births that could not be geocoded. Cancer cases and controls were frequency matched (1:3) by birth year. Sociodemographic and birth characteristics data were extracted for analysis, along with maternal addresses at birth that were geocoded. Cancer types were designated according to the International Classification of Childhood Cancer and Adolescent and Young Adult site recode definitions. The study was reviewed and approved by the Institutional Review Boards at the California Department of Public Health, the University of California, Berkeley, and the University of California, Irvine.

Per- and polyfluoroalkyl substances exposure measurements

The UCMR3 included PFAS monitoring data for 455 water systems in California. Exposure measures were derived from the UCMR3 monitoring data for the 26 public water systems in California with detectable levels of PFOS or PFOA (Figure 1). PFOS and PFOA were more frequently detected in California than the other PFAS, and therefore we restricted our analyses to PFOS and PFOA exposures. Service area boundaries of public water systems serving California were downloaded as a shapefile from the CA State Geoportal.[24] Maternal residences at birth were linked to corresponding water district boundaries using ESRI ArcMap 10.8.2 (Redlands, CA).

The concentrations detected in water were used to calculate prenatal exposure to steady-state concentrations present in maternal serum, assuming long-term exposure. Measured maternal serum PFAS is correlated to PFAS concentrations measured in infant and child serum.[25,26] For each of the 26 public water systems, the analytical detection values of PFOS and PFOA from 2013 to 2015 were averaged. The average detected levels of PFOS or PFOA were used as inputs for a one-compartment pharmacokinetic model[27] with a constant exposure rate in order to predict the average steady-state maternal serum concentrations expected for a mother that resided in an area served by a specific public water system. The model considers biological sex and menstrual status as parameters, and serum was predicted for females who were of childbearing age. The half-lives used for PFOS and PFOA were 3 and 2 years, respectively, and were based on the calculated half-lives of PFOS[28] and PFOA[29] with a physiologic adjustment for blood loss due to menses. PFOS and PFOA serum contribution from other nondrinking water background exposures were 5.2 ng/ml and 1.67 ng/ml, respectively, using published values for those aged 20 and older from the National Health and Nutrition Examination Survey years 2015–2016.[30] Mothers with California birth addresses outside of contaminated water district boundaries were assigned serum levels of PFOS and PFOA consistent with what would be expected from background exposure levels of PFOS or PFOA without additional exposure through drinking water.

Statistical analyses

Descriptive analyses were completed using chi-squared tests to analyze differences between the cases and controls regarding their sociodemographic characteristics. The correlation between predicted PFOS and PFOA serum concentrations was calculated using Pearson's *r*.

We applied logistic regression models to calculate adjusted odds ratios (AORs) and 95% confidence intervals (CIs) for

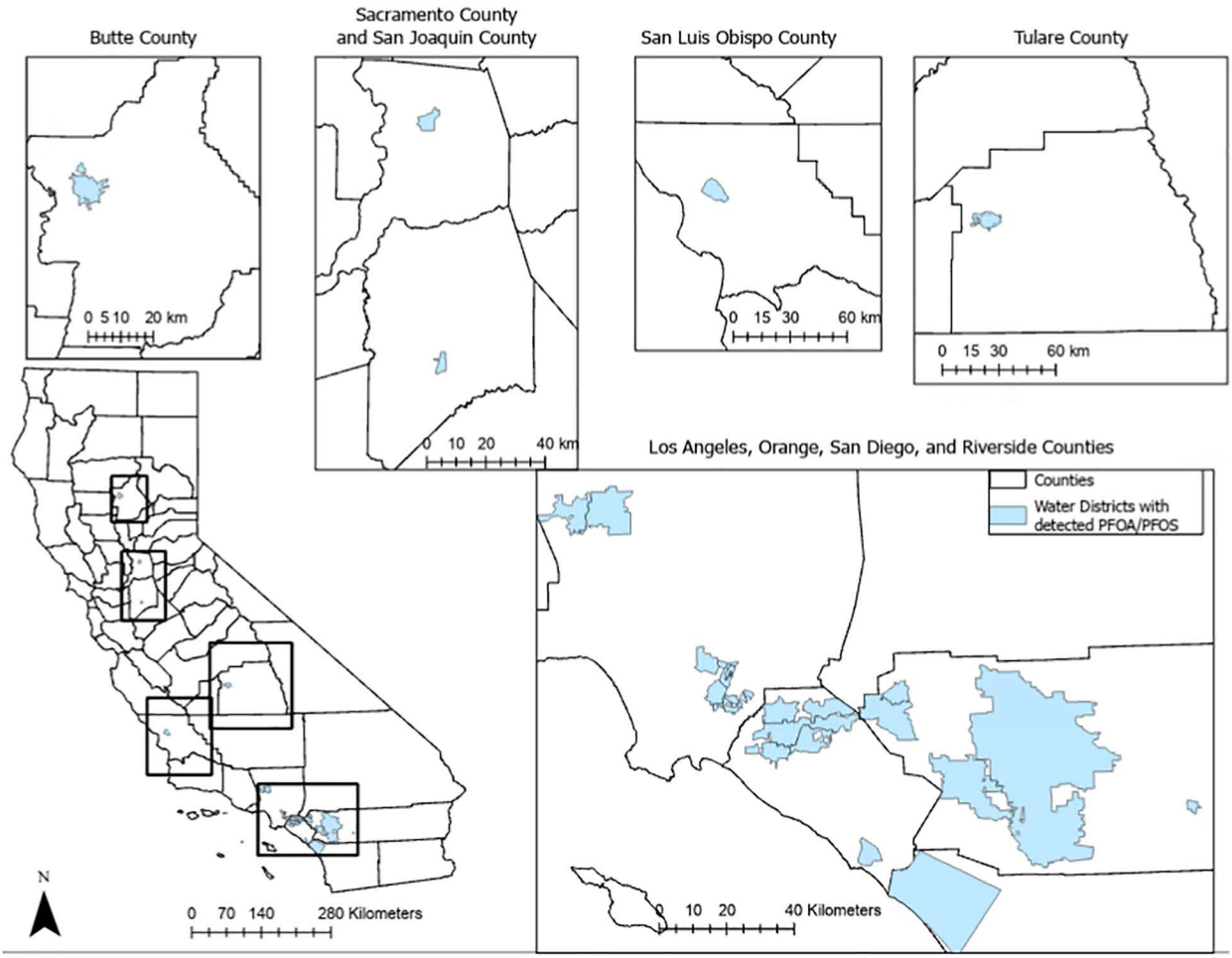

Figure 1. Map of study area. The study area includes CALSEC cases and controls with maternal addresses at birth in California (2000–2015). PFOS and PFOA exposures from drinking water were based on residence in an area served by one of 26 public water systems in California with detectable levels reported in the UCMR3 (2013–2015).

each cancer type or group using R version 4.3.2 (R Project for Statistical Computing, Vienna, Austria). Based on the available data, only cancer types or groups with more than 90 cases were analyzed to ensure sufficient numbers for analysis.[31] Types with less than 90 cases were either extremely rare (much less than 90) or of unspecified or other categories, which would be difficult to interpret. Recurrent cases of the same cancer were excluded from analysis while retaining the first occurrence and diagnosis year for an individual (n = 43). Prenatal maternal serum PFOS and PFOA concentrations were modeled as continuous exposure measures in independent models since predicted PFOS and PFOA serum concentrations were correlated (r = 0.72, P < 0.001). We report AORs and 95% CIs associated with an increase of 5 ng/ml PFOS and 2 ng/ml PFOA, which is the equivalent of a doubling of background exposure.

Model covariates were selected due to known or suspected associations with childhood cancer, exposure to PFAS from public water systems, and/or maternal PFAS concentrations. The relationships between the exposure, outcome, and covariates are shown in a directed acyclic graph (Figure 2). We first conducted an analysis only adjusted for birth year (matching factor), and then a fully adjusted analysis that included sex (male, female, undetermined), insurance provider for prenatal care (private, Medicare/Medi-Cal, or unknown), maternal race and ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian American and Pacific Islander, non-Hispanic American Indian, or other/unknown), maternal birthplace (US born or not-US born), maternal age (discrete variable), and maternal education (8th grade or less, 9–12th grade, at least some college, and unknown).

We conducted stratified analyses based on maternal birthplace (US born and Mexico born) for cancers with at least 500 total cases, in order to have at least 90 cases in each strata. This included overall leukemias (n = 3,460), acute lymphoid leukemia (n = 2,820), acute myeloid leukemia (n = 500), overall lymphomas (n = 537), noncentral system embryonal tumors (n = 2,880), all brain tumors (n = 1,590), astrocytoma (n = 789), specified low-grade astrocytic tumors (n = 565), Wilms tumor (n = 556), and neuroblastoma (n = 766). We also performed this stratified analysis for retinoblastoma cases (n = 399) in order to compare our results with another published PFAS exposure and retinoblastoma analysis.[11] Finally, we conducted a subset analysis for children born 2010–2015 to coincide with the UCMR3 data collection period.

Results

Cases and controls were similar in maternal age and maternal education; however, cases were more likely to have private insurance, have US-born mothers, and have non-Hispanic White mothers than the controls (Table 1). Details regarding exposure assignments derived from UCMR3 data are provided in Table 2. Predicted mean serum levels among cases and controls exposed to PFOS through drinking water were 12.4 ng/ml. Regarding

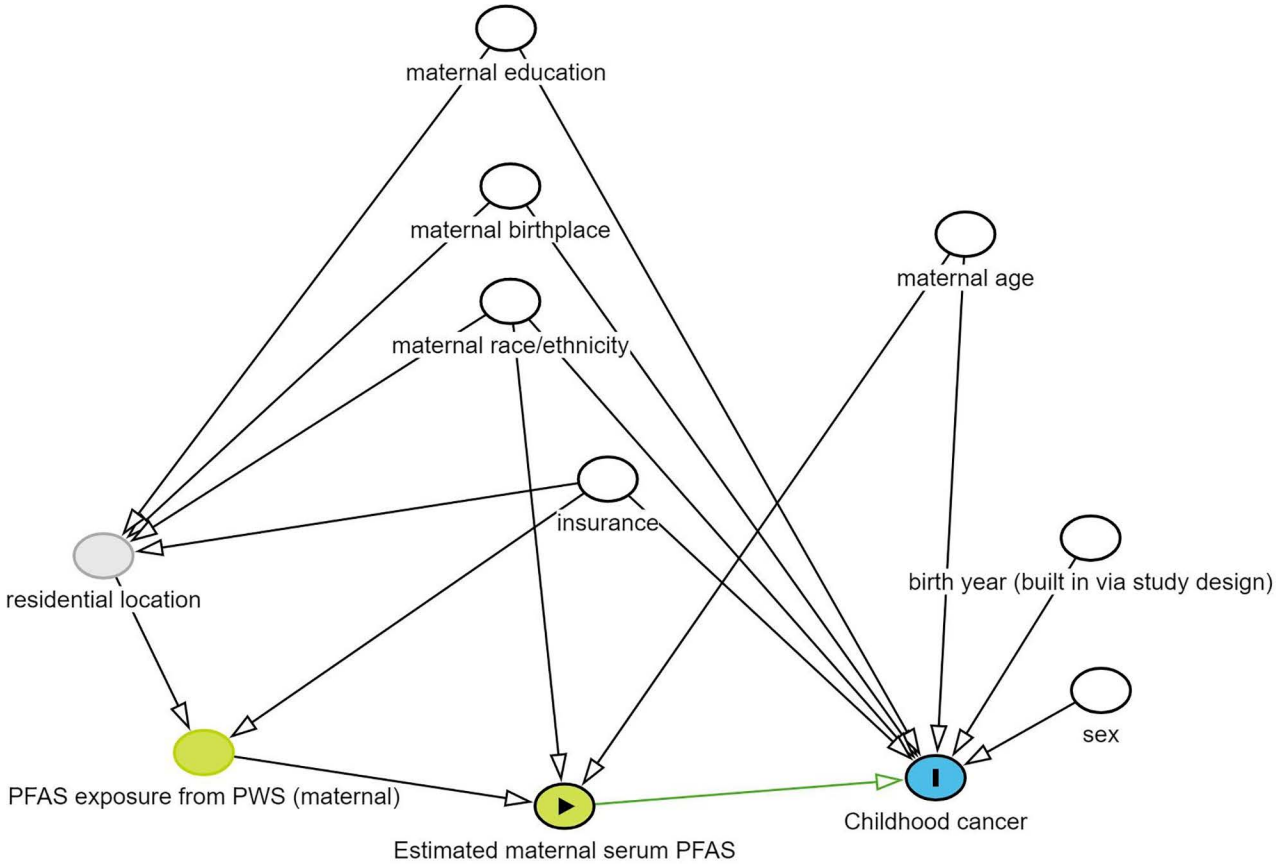

Figure 2. Directed acyclic graph (DAG) conceptualizing the plausible relationships between potential confounders of the association between estimated maternal serum PFAS concentration (exposure) and childhood cancer (outcome). Yellow = ancestor of exposure; gray = unmeasured confounder; white = controlled for in analyses.

PFOA, mean serum levels among cases (5.28 ng/ml) and controls (5.23 ng/ml) were similar. Predicted prenatal PFOS maternal serum concentrations ranged from 5.0 ng/ml (background) to 22.89 ng/ml. Predicted prenatal PFOA maternal serum concentrations ranged from 2.0 ng/ml (background) to 6.66 ng/ml. Details of the contaminated water districts are presented in Supplemental Table 1; http://links.lww.com/EE/A320. The Eastern Municipal Water District served 798 CALSEC cases and controls and had the highest average PFOA levels reported in the UCMR3 data (0.0485 µg/l), while CA American Water Co. – Suburban served 64 cases and controls and had the highest average PFOS levels (0.1550 µg/l). The majority (92%) of birth addresses for CALSEC cases and controls were not located in public water systems with UCMR3-detectable PFOS or PFOA contamination and therefore were assigned background exposure serum levels; 11% of addresses were in ZIP codes not served by any public water system included in UCMR3 monitoring. Predicted average concentrations of PFOS (~5.6 ng/ml) and PFOA (~2.2 ng/ml) were similar among US-born and Mexico-born mothers.

Adjusted models showed suggestive increased risks of some cancer types associated with PFOS and PFOA exposures (Table 3). The odds ratios (ORs) derived from the multivariable-adjusted models are similar to ORs from models adjusted only for the matching factor of the birth year (Supplemental Table 2; http://links.lww.com/EE/A320). Positive associations were seen between PFOS levels and nonastrocytoma glioma (AOR = 1.26; 95% CI: 0.99, 1.60) and noncentralsystem embryonal tumors all combined (AOR = 1.07; 95% CI: 0.98, 1.17) including neuroblastoma (AOR = 1.12; 95% CI: 0.95, 1.31) and Wilms tumor (AOR = 1.15; 95% CI: 0.96, 1.38), as well as with acute myeloid leukemia (AOR = 1.14; 95% CI: 0.94, 1.39). PFOS models also showed suggestive evidence of a decreased risk of astrocytoma (AOR = 0.90; 95% CI: 0.74, 1.09). Among Mexico-born mothers, PFOS exposure was positively associated with noncentral system embryonal tumors (AOR = 1.24; 95% CI: 1.03, 1.50) and Wilms tumor (AOR = 1.52; 95% CI: 1.06, 2.18) (Table 4). The tests for heterogeneity comparing maternal birthplace (US born, Mexico born, or other) for noncentral system embryonal tumors and Wilms tumors were not statistically significant (P = 0.17 and 0.20, respectively). PFOS results of the subset analysis among children born 2010–2015 were null (Supplemental Table 3; http://links.lww.com/EE/A320).

For PFOA, there was a suggestion of increased risks of non-Hodgkin lymphoma (NHL) (AOR = 1.19; 95% CI: 0.95, 1.49) and noncentral system embryonal tumors (AOR = 1.04; 95% CI: 0.95, 1.14) (Table 3). There was also suggestive evidence of decreased risk for astrocytoma (AOR = 0.84; 95% CI: 0.67, 1.03). Among Mexico-born mothers, PFOA exposure was positively associated with Wilms tumor (AOR = 1.59; 95% CI: 1.12, 2.24) and noncentral system embryonal tumors (AOR = 1.19; 95% CI: 0.98, 1.45) (Table 4). The tests for heterogeneity comparing maternal birthplace (US born, Mexico born, or other) for noncentral system embryonal tumors and Wilms tumors were again not statistically significant (P = 0.32 for both). PFOA results of the subset analysis among children born 2010–2015 were null (Supplemental Table 3; http://links.lww.com/EE/A320).

Discussion

In this population-based study, the first in the US to examine the risk of developing childhood cancer types in relation to estimated prenatal maternal PFOA and PFOS exposures through

Table 1.

Characteristics of cases and controls in the California Linkage Study of Early-onset Cancers (CALSEC) with maternal addresses at birth in California, 2000–2015

Characteristic	n cases	% cases	n controls	% controls	*P* value
Birth year					0.89
2000–2004	4,758	46.56	13,878	46.30	
2005–2009	3,596	35.19	10,579	35.29	
2010–2015	1,866	18.26	5,517	18.41	
Maternal age (years)					<0.001
13–19	815	7.97	2,723	9.08	
20–24	2,065	20.21	6,745	22.50	
25–29	2,672	26.14	7,878	26.28	
30–34	2,689	26.31	7,548	25.18	
35–39	1,535	15.02	4,028	13.44	
40+	444	4.34	1,052	3.51	
Maternal education					<0.001
8th grade or less	754	7.38	2,905	9.69	
9–12th grade	4,309	42.16	12,951	43.21	
Some college	4,870	47.65	13,310	44.41	
Unknown	287	2.81	808	2.70	
Sex					<0.001
Female	4,701	46.00	14,668	48.94	
Male	5,519	54.00	15,305	51.06	
Undetermined	0	0.00	1	0.00	
Insurance					<0.001
Private	5,768	56.44	14,863	49.59	
Medicare/medical	4,012	39.26	13,416	44.76	
Other/unknown	440	4.31	1,695	5.65	
Maternal race and ethnicity					<0.001
Non-Hispanic White	3,558	34.81	8,798	29.35	
Non-Hispanic Black	505	4.94	1,675	5.59	
Hispanic	4,844	47.40	15,145	50.53	
Asian American and Pacific Islanders	1,118	10.94	3,828	12.77	
Non-Hispanic American Indian	44	0.43	140	0.47	
Other/unknown	151	1.48	388	1.29	
Maternal birthplace					<0.001
United States	6,199	60.66	16,490	55.01	
Mexico	2,226	21.78	7,723	25.77	
Other	1,795	17.56	5,761	19.22	

Table 2.

Serum levels for cases and controls with drinking water exposure

	PFOS (ng/ml)		PFOA (ng/ml)	
	Cases (n = 754)	Controls (n = 2,173)	Cases (n = 558)	Controls (n = 1,647)
Mean (SD)	12.4 (2.56)	12.4 (2.56)	5.28 (1.14)	5.23 (1.13)
Median (25th percentile, 75th percentile)	11.1 (10.7, 14.5)	11.1 (10.7, 14.5)	5.0 (4.16, 6.66)	5.0 (4.12, 6.66)
Minimum	9.9	9.9	3.83	3.83
Maximum	22.9	22.9	6.66	6.66

Unexposed cases (n = 9,406) and controls (n = 27,461) were assigned to 5 ng/ml PFOS and 2 ng/ml PFOA to be representative of serum concentrations from background levels of exposure to PFOS and PFOA.

drinking water, we observed positive associations with Wilms tumor, particularly among children with Mexico-born mothers. While elevated risks of other cancers were observed, such as other glioma, other embryonal tumors, and NHL, associations were not consistent and CIs included one. Nonsignificant inverse associations with astrocytoma and germ cell neoplasms were also observed. Overall, results were generally null, and both positive and inverse findings could have been due to chance.

Wilms tumor is the most common pediatric kidney cancer and the fourth most common pediatric cancer overall.[32] Rare in adults, the average age at diagnosis of Wilms tumor is between 3 and 5 years old.[32] Although no other studies to our knowledge have examined the association between PFAS exposure and Wilms tumors, in meta-analyses of adult cancers, an average relative increase in kidney cancer risk per 10 ng/ml increase in serum PFOA was 16%,[33] and an International Agency for Research on Cancer working group concluded that there was "limited" evidence for RCC in humans in their finalized evaluation in 2023.[9] While the etiologies of childhood Wilms tumor and adult RCC are distinct, there are mechanistic data supporting a possible association between PFAS and cancers of the kidney. PFAS exposure has been found to cause notable histologic and cellular changes including oxidative stress in the kidney,[34] which could be related to the development of kidney cancers. In contrast to our findings, another study found a reduced risk for Wilms tumor among California-born children of non-US-born Hispanic mothers (hazard ratio: 0.70; 95% CI: 0.59–0.82).[35] Wilms tumors have been associated with prenatal maternal exposures to pesticides.[36] Evidence regarding the association between PFAS and pesticides is mixed; while PFOS was detected in various insecticide products,[37] no PFOS was detected upon a verification analysis of the same products.[38] While we do not

Table 3.

Adjusted odds ratios and 95% confidence intervals for associations between predicted maternal serum concentrations of PFOS and PFOA and childhood cancer types, as defined by International Classification of Childhood Cancer and Adolescent and Young Adult site recode definitions, in CALSEC participants (2000–2015)

Cancer type	n	PFOS AOR (95% CI)	*P* value	PFOA AOR (95% CI)	*P* value
Leukemias[a]	3,460	0.98 (0.90, 1.07)	0.73	0.99 (0.90, 1.08)	0.82
Acute lymphoid leukemia	2,820	0.95 (0.86, 1.04)	0.27	0.98 (0.89, 1.08)	0.70
Acute myeloid leukemia	500	1.14 (0.94, 1.39)	0.17	1.02 (0.81, 1.27)	0.88
Lymphomas[b]	537	1.00 (0.81, 1.24)	0.99	1.07 (0.87, 1.32)	0.52
Non-Hodgkin lymphoma	384	1.08 (0.85, 1.37)	0.51	1.19 (0.95, 1.49)	0.14
Hodgkin lymphoma	153	0.78 (0.48, 1.27)	0.32	0.72 (0.42, 1.26)	0.26
All brain tumors[c]	1,590	0.98 (0.87, 1.11)	0.77	0.96 (0.84, 1.09)	0.52
Astrocytoma[d]	789	0.90 (0.74, 1.09)	0.28	0.83 (0.67, 1.03)	0.09
Specified low-grade astrocytic tumors	565	0.95 (0.76, 1.17)	0.61	0.87 (0.69, 1.10)	0.25
Glioblastoma and anaplastic astrocytoma	127	0.90 (0.57, 1.44)	0.66	0.82 (0.48, 1.40)	0.47
Astrocytoma, NOS	97	0.59 (0.28, 1.26)	0.17	0.57 (0.25, 1.31)	0.19
Other glioma	268	1.26 (0.99, 1.60)	0.06	1.16 (0.89, 1.52)	0.28
Ependymoma	177	0.96 (0.66, 1.39)	0.81	1.06 (0.74, 1.51)	0.77
Medulloblastoma and other PNET[e]	356	0.93 (0.72, 1.22)	0.62	1.00 (0.77, 1.29)	0.97
Medulloblastoma	221	1.03 (0.76, 1.41)	0.85	1.08 (0.80, 1.47)	0.60
Supratentorial PNET	135	0.77 (0.46, 1.27)	0.30	0.83 (0.51, 1.37)	0.48
Osseous and chondromatous neoplasms					
Osteosarcoma	122	1.27 (0.88, 1.83)	0.20	1.19 (0.79, 1.78)	0.41
Ewing tumor	113	0.77 (0.44, 1.36)	0.37	0.98 (0.61, 1.59)	0.94
Soft tissue sarcomas					
Rhabdomyosarcoma	304	1.05 (0.80, 1.37)	0.74	0.94 (0.70, 1.28)	0.7
Germ cell and trophoblastic neoplasms[f]	311	0.80 (0.57, 1.12)	0.19	0.86 (0.62, 1.20)	0.37
Germ cell and trophoblastic neoplasms of gonads (female)	69	1.14 (0.61, 2.12)	0.68	1.16 (0.62, 2.17)	0.65
Germ cell and trophoblastic neoplasms of gonads (male)	53	0.72 (0.33, 1.55)	0.40	0.35 (0.07, 1.65)	0.18
Germ cell and trophoblastic neoplasms of nongonadal sites[g]	189	0.73 (0.46, 1.15)	0.18	0.90 (0.60, 1.35)	0.61
Carcinomas[h]	204	1.07 (0.77, 1.49)	0.67	0.77 (0.49, 1.22)	0.27
Thyroid carcinoma	95	1.21 (0.78, 1.87)	0.41	0.90 (0.50, 1.63)	0.74
Miscellaneous specified neoplasms, NOS					
Wilms tumor	556	1.15 (0.96, 1.38)	0.14	1.11 (0.92, 1.34)	0.29
Neuroblastoma	766	1.12 (0.95, 1.31)	0.17	1.07 (0.90, 1.26)	0.46
Other pediatric and embryonal tumors, NOS	417	1.00 (0.79, 1.26)	0.97	0.96 (0.74, 1.24)	0.75
Retinoblastoma	399	1.07 (0.86, 1.34)	0.54	1.01 (0.79, 1.29)	0.95
Myeloma, mast cell, miscellaneous lymphoreticular neoplasms, NOS	324	1.03 (0.80, 1.33)	0.81	0.88 (0.65, 1.20)	0.42
Noncentral system embryonal tumors[i]	2,880	1.07 (0.98, 1.17)	0.13	1.04 (0.95, 1.14)	0.38

Adjusted for birth year, sex, maternal race and ethnicity, maternal birthplace, maternal age, maternal education, and insurance type.

[a]Children diagnosed with: acute lymphoid leukemia, acute myeloid leukemia, chronic myeloid leukemia, and other and unspecified leukemia.

[b]Children diagnosed with: non-Hodgkin lymphoma and Hodgkin lymphoma.

[c]Children diagnosed with: specified low-grade astrocytic tumors, glioblastoma and anaplastic astrocytoma, astrocytoma, NOS, other glioma, ependymoma, medulloblastoma, and supratentorial PNET.

[d]Children diagnosed with: specified low-grade astrocytic tumors, glioblastoma and anaplastic astrocytoma, and astrocytoma, NOS.

[e]Children diagnosed with: medulloblastoma and supratentorial PNET.

[f]Children diagnosed with: germ cell and trophoblastic neoplasms of gonads, intracranial (all behaviors), and other nongonadal.

[g]Children diagnosed with: intracranial (all behaviors) and other nongonadal.

[h]Children diagnosed with: thyroid carcinoma, nasopharyngeal carcinoma, other sites in lip, oral cavity and pharynx, carcinoma of trachea, bronchus, and lung, carcinoma of kidney, carcinoma of bladder, carcinoma of gonads, carcinoma of colon and rectum, carcinoma of stomach, carcinoma of liver and intrahepatic bile ducts, carcinoma of pancreas, carcinoma of other and ill-defined sites, gastrointestinal tract, adrenocortical carcinoma, and carcinoma of other and ill-defined sites, NOS.

[i]Children diagnosed with: osteosarcoma, chondrosarcoma, Ewing tumor, other specified and unspecified bone tumors, fibromatous neoplasms, rhabdomyosarcoma, specified soft tissue sarcoma (excluding Kaposi sarcoma), Kaposi sarcoma, unspecified soft tissue sarcoma, Wilms tumor, neuroblastoma, and other pediatric and embryonal tumors, NOS.

NOS, not otherwise specified; PNET, primitive neuroectodermal tumors.

control for pesticide exposure in this analysis, it is unlikely to be correlated to PFAS exposure via drinking water. PFAS exposures in this study are likely from recharged wastewater and therefore PFAS exposures from pesticide use represent a different potential exposure source.

We found that the odds of retinoblastoma were slightly elevated in association with PFOS exposure (AOR = 1.07; 95% CI: 0.86, 1.34), but not associated with PFOA exposure (AOR = 1.01; 95% CI: 0.79, 1.29). Our results are in contrast to that of another California study, where above-mean PFOS levels at birth increased the odds of retinoblastoma (AOR = 1.29; 95% CI: 1.00, 1.67) and unilateral retinoblastoma (AOR = 1.42; 95% CI: 1.03, 1.97), with exposures determined from measured PFOA and PFOS in newborn dried blood spots.[11] This study included 501 childhood retinoblastoma cases diagnosed at or before age 5 and 899 controls, with both cases and controls born between 1983 and 2011,[11] whereas in our study, cases were diagnosed at or before age 15 and born from 2000 to 2015. In the other study, when stratifying by maternal birthplace, an above-mean PFOS measure was associated with unilateral retinoblastoma in children of US-born mothers (AOR = 1.71; 95% CI: 1.04, 2.90), retinoblastoma overall in children of Mexico-born mothers (AOR = 1.67; 95% CI: 1.06, 2.66), and bilateral retinoblastoma in children of Mexico-born mothers (AOR = 2.06; 95% CI: 1.12, 3.92);[11] we saw similar results for Mexico-born mothers. Above-mean PFOA increased the odds of overall retinoblastoma among children of US-born mothers (AOR = 1.41; 95% CI: 1.00, 2.02),[11] however, we observed a null association in our analysis.

Regarding acute lymphoid leukemia, AORs in the current study were not elevated (AOR = 0.95; 95% CI: 0.86, 1.04 for PFOS exposure and AOR = 0.98; 95% CI: 0.89, 1.08 for PFOA exposure). In a Finnish study, PFOS and PFOA concentrations were measured in first-trimester maternal serum samples

Table 4.

Adjusted odds ratios and 95% confidence intervals for associations between predicted maternal serum concentrations of PFOS and PFOA and childhood cancer types in CALSEC participants (2000–2015), stratified by maternal birthplace

Cancer type	n	PFOS AOR (95% CI)	*P* value for interaction	PFOA AOR (95% CI)	*P* value for interaction
Leukemias[a]	3,460				
United States	1,976	1.02 (0.92, 1.14)	0.45	1.03 (0.93, 1.15)	0.69
Mexico	862	0.87 (0.72, 1.05)	0.09	0.85 (0.69, 1.05)	0.15
Noncentral system embryonal tumors[b]	2,880				
United States	1,834	1.04 (0.93, 1.15)	0.66	1.01 (0.90, 1.13)	0.87
Mexico	557	1.24 (1.03, 1.50)	0.17	1.19 (0.98, 1.45)	0.32
Acute lymphoid leukemia	2,820				
United States	1,613	1.01 (0.89, 1.13)	0.81	1.03 (0.92, 1.16)	0.83
Mexico	722	0.80 (0.64, 1.00)	0.15	0.82 (0.65, 1.04)	0.17
All brain tumors[c]	1,590				
United States	1,036	0.99 (0.85, 1.15)	0.35	0.92 (0.79, 1.09)	0.74
Mexico	292	1.08 (0.82, 1.42)	0.24	1.09 (0.83, 1.45)	0.69
Astrocytoma[d]	789				
United States	519	0.90 (0.72, 1.13)	0.97	0.81 (0.63, 1.04)	0.38
Mexico	136	0.88 (0.56, 1.39)	0.94	0.83 (0.50, 1.39)	0.59
Neuroblastoma	766				
United States	523	1.07 (0.88, 1.29)	0.82	1.01 (0.82, 1.23)	0.42
Mexico	115	1.34 (0.92, 1.95)	0.63	1.29 (0.88, 1.90)	0.97
Specified low-grade astrocytic tumors	565				
United States	378	0.96 (0.75, 1.24)	0.79	0.84 (0.63, 1.12)	0.16
Mexico	92	0.80 (0.44, 1.44)	0.54	0.77 (0.40, 1.50)	0.26
Wilms tumor	556				
United States	373	1.08 (0.87, 1.35)	0.62	0.98 (0.77, 1.26)	0.79
Mexico	101	1.52 (1.06, 2.18)	0.20	1.59 (1.12, 2.24)	0.32
Lymphomas[e]	537				
United States	311	0.91 (0.68, 1.21)	0.89	1.05 (0.81, 1.36)	0.53
Mexico	110	1.39 (0.95, 2.04)	0.21	1.31 (0.87, 1.97)	0.29
Acute myeloid leukemia	500				
United States	283	1.11 (0.86, 1.42)	0.26	1.09 (0.84, 1.41)	0.86
Mexico	108	1.05 (0.66, 1.67)	0.28	0.80 (0.43, 1.48)	0.57
Retinoblastoma	399				
United States	241	1.03 (0.78, 1.37)	0.71	1.00 (0.75, 1.35)	0.80
Mexico	89	1.25 (0.81, 1.93)	0.47	1.05 (0.63, 1.74)	0.80

Models stratified by mother's birth country, and adjusted for birth year, sex, maternal race and ethnicity, maternal age, maternal education, and insurance type. Reported *P* values are from interaction model terms for the interaction between predicted serum PFOS or PFOA and mother's birth country.

[a]Children diagnosed with: acute lymphoid leukemia, acute myeloid leukemia, chronic myeloid leukemia, and other and unspecified leukemia.

[b]Children diagnosed with: osteosarcoma, chondrosarcoma, Ewing tumor, other specified and unspecified bone tumors, fibromatous neoplasms, rhabdomyosarcoma, specified soft tissue sarcoma (excluding Kaposi sarcoma), Kaposi sarcoma, unspecified soft tissue sarcoma, Wilms tumor, neuroblastoma, and other pediatric and embryonal tumors, NOS.

[c]Children diagnosed with: specified low-grade astrocytic tumors, glioblastoma and anaplastic astrocytoma, astrocytoma, NOS, other glioma, ependymoma, medulloblastoma, and supratentorial PNET.

[d]Children diagnosed with: specified low-grade astrocytic tumors, glioblastoma and anaplastic astrocytoma, and astrocytoma, NOS.

[e]Children diagnosed with: non-Hodgkin lymphoma and Hodgkin lymphoma.

NOS, not otherwise specified; PNET, primitive neuroectodermal tumors.

collected from 1986 to 2010 of 400 acute lymphoblastic leukemia cases younger than 15 years old and 400 controls.[12] An association between PFOS and acute lymphoblastic leukemia was seen when the analysis was restricted to samples collected in 1986–1995, in which mean PFOS levels were the highest (median = 17.9 µg/l) ($OR_{perlog2}$ = 4.01; 95% CI: 1.62, 9.93).[12] When comparing our predicted serum concentrations to that of this Finnish study, both median PFOA (3.17 µg/l) and PFOS (11.83 µg/l) were higher in the Finnish cohort than the means in our California cohort. The measured serum concentrations in the Finnish cohort were also representative of PFAS exposure from all sources, while the serum concentrations in our study were predicted based on exposures from PFAS-contaminated drinking water.

Among the other cancer types identified in clusters near PFAS-contaminated sites, acute myeloid leukemia was positively associated with PFOS exposure in the current study (AOR = 1.14; 95% CI: 0.94, 1.39). The results for the other cancer types identified in clusters (rhabdomyosarcoma and brain tumors) were null in relation to both PFOA and PFOS exposures in our study; while other studies identified clusters of these cancer types, their subsequent analyses to further investigate these clusters were not restricted to childhood cancers.[13–15] While a cancer cluster occurs when there are more cancer cases than expected at a given region and time, the appearance of cancer clusters may be due to chance rather than a specific cause.[39]

Strengths of our study include the high reporting rate of cancer incidence to the California Cancer Registry, which minimizes the chance of selection bias, and the large sample size across multiple cancer types. The use of PFOA and PFOS concentrations in drinking water to estimate maternal serum concentrations allowed us to assess these associations for a large population across the state of California. The results were suggestive of an association between PFOS and PFOA exposure and noncentral system embryonal tumors; between PFOS and acute myeloid leukemia, Wilms tumor, neuroblastoma, and nonastrocytoma gliomas; and between PFOA and NHL. Our analysis is limited in that we performed multiple testing using the CALSEC dataset for each cancer, which could result in false positive findings.

The exposure assessment is limited by the use of modeled prenatal maternal PFOA and PFOS exposures derived from UCMR3 data. We assume that prenatal measures are correlated with modeled predictions given the long half-lives of

PFOA and PFOS. Further, exposure assignments also relied on PFAS detections in public water systems during the years 2013–2015, although participants were born between 2000 and 2015. Because PFOS and PFOA have been phased out of production, there is potential for higher concentrations of PFOS and PFOA in public water systems in earlier years that were not accounted for in our analyses. The use of UCMR3 data may not represent point-of-use exposure from an individual tap, and it does not capture potential exposures for those using private well water. However, as of 2015, 96% of California's population used public water supplies for domestic use.[40] In another study that analyzed tap water samples for PFAS, at least one PFAS was detected in 40% of public-supply samples, compared with 4% of water districts with PFAS detected in the UCMR3[41]; however, the UCMR3 had higher detection limits, which likely contributed to this observed difference. While the lack of individual tap water measurements is a limitation in the exposure assessment, this would likely contribute to nondifferential exposure misclassification that would bias our results toward the null. These exposure measures are also based on birth address; if the mother moved to an area served by a different public water system for the majority of the pre- or postnatal exposure window, residence at birth may not be the most appropriate location to derive exposure measures. Assigning exposures based on geocoded residences and water monitoring data under the assumption that mothers of CALSEC children consume tap water rather than bottled water may result in some exposure misclassification, but the misclassification is likely nondifferential to case status and would bias results toward the null. Furthermore, previous studies of PFOA exposure showed that the findings were relatively insensitive to the individual exposure assignments when the rank order of contamination across water districts was correct.[42,43] We also assumed that the mothers who resided in other water districts at the time of the child's birth were not exposed to PFAS above background levels, which may not be true.

In conclusion, this is one of the first studies to assess prenatal exposures to PFOS or PFOA and the associations with the incidence of multiple childhood cancer types by specifically assessing the epidemiologic impacts of exposures to PFAS via drinking water. This study design is unique compared to others that used exposure measures derived from biomarkers representing overall PFAS exposures from unknown sources. Our results are relevant in the context of the EPA's national PFAS drinking water standard, and this analysis may help determine if reduced PFAS exposure via drinking water regulations decreases childhood cancer incidence in California. If mothers were exposed to 4 ng/l PFOS or PFOA in drinking water per the 2024 EPA standard, their steady-state serum concentrations are predicted to be 5.66 ng/ml PFOS and 2.08 ng/ml PFOA, comparable to that of experiencing background exposure only. Our research contributes to the sparse literature on childhood cancers explored in previous epidemiologic studies, and the results suggest that there are several cancer types associated with prenatal PFAS exposures. Additional studies are warranted to investigate these relationships further.

Conflicts of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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